PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
KENF/P23194PC		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/03660	25/09/2000	24/09/1999
International Patent Classification (IPC) or national classification and IPC A61K39/00		
Applicant THE MATHILDA AND TERENCE KENNEDY INSTITUTE OF ...		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 11 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 8 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18/04/2001	04.03.2002
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer K. Muller-Thomalla Telephone No. +31 70 340 4230

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/03660

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-79	as originally filed				

Claims, No.:

1-48	as received on	14/01/2002	with letter of	11/01/2002	

Drawings, sheets:

1/9-9/9	as originally filed				

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. whole of claims 1-6,28,47,48 with respect to IA and part of claims 1-6 and 24-48 with respect to N and IS.

because:

   ☒ the said international application, or the said claims Nos. 1-6,28,47,48 (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. Part of claims 1-6 and 24-48.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☒ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-23,25-44,46-48
	No:	Claims	24,45
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-48
Industrial applicability (IA)	Yes:	Claims	7-27,29-46
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Reference is made to the following documents:

D1: FOXWELL BRIAN ET AL: "Efficient adenoviral infection with IkappaBalpha reveals that macrophage tumor necrosis factor alpha production in rheumatoid arthritis is NF-kappaB dependent." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 95, no. 14, 7 July 1998 (1998-07-07), pages 8211-8215, July 7, 1998 ISSN: 0027-8424

D2: EIGLER A ET AL: "Taming TNF: strategies to restrain this proinflammatory cytokine" IMMUNOLOGY TODAY,GB,ELSEVIER PUBLICATIONS, CAMBRIDGE, vol. 18, no. 10, 1 October 1997 (1997-10-01), pages 487-492, ISSN: 0167-5699

D3: SEBBAG M ET AL: "Cytokine stimulation of T lymphocytes regulates their capacity to induce monocyte production of tumor necrosis factor-alpha, but not interleukin-10: possible relevance to pathophysiology of rheumatoid arthritis." EUROPEAN JOURNAL OF IMMUNOLOGY, (1997 MAR) 27 (3) 624-32. ,

D4: CHABOT S ET AL: "Microglial production of TNF - alpha is induced by activated T lymphocytes. Involvement of VLA-4 and inhibition by interferonbeta-1b." JOURNAL OF CLINICAL INVESTIGATION, (1997 AUG 1) 100 (3) 604-12.

D5: AVICE M N ET AL: "Lymphocyte activation gene-3, a MHC class II ligand expressed on activated T cells, stimulates TNF - alpha and IL-12 production by monocytes and dendritic cells." JOURNAL OF IMMUNOLOGY, (1999 MAR 1) 162 (5) 2748-53.

D6: US 5 085 985 A (MAINO VERNON C ET AL) 4 February 1992 (1992-02-04)

D7: MACLEAN J A ET AL: "Anti -CD3: anti - IL - 2 receptor bispecific monoclonal antibody. Targeting of activated T cells in vitro." JOURNAL OF IMMUNOLOGY, (1993 FEB 15) 150 (4) 1619-28.

See in particular those passages cited as relevant in the International Search Report.

section III

1. Claims 1-6,28,47 and 48 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject- matter of these claims (Article 34(4)(a)(i) PCT).

2. With respect to the subject-matter of part of claims 1-6 and 24-48 examined in the present IPER, please see International Search Report Box 3, ISA Form/206 relating to the observations on claimed subject-matter found unsearchable and sections V and VIII below.

section IV

The amended claims 1-48 are now considered to satisfy the conditions of unity of invention.

section V

1. The present invention according to amended claims 1-48 relates to treatment of chronic inflammatory disease comprising the administration of an inhibitor of cytokine activated T cells (designated as Tck cells) opposed to TRC activated cells (e.g. by anti-CD3 antibodies). The only claimed inhibitors searched are nf-kappa inhibitors such as IkappaBalpha and antibodies having specificity for generally activated T- cells.

2. The present application does not satisfy the requirements of Article 33(2)PCT for lack of novelty of claims 24 and 45 in the light of the cited prior art (see in e.g.D1 which discloses compounds which have efficacy in the treatment of chronic inflammatory disease such as nf-kappa inhibitors, for instance IkappaBalpha). Whether the compound has been identified according to a certain method (in this case the method according to any one of claims 7-23) does not confer any novel **defined** technical features to the known compound and therefore does not contribute in establishing the required novelty according to Article 33(2) PCT.

3. The remaining claims might formally satisfy the requirements of Article 33(2) PCT but nevertheless contravene Article 33(3) PCT:
(With respect to the novelty of any claims relating to Tck-cell specific antibodies see section VIII below).

3.1 Claim 1 was amended to include a further functional feature defined in terms of a physiological effect to be achieved by the administration of a compound that "selectively" inhibits Tck cells, that is by rendering the Tck cells functionally inhibited with respect to their ability to activate monocytes and/or by reducing the number of the Tck cells.
This newly added functional feature cannot be taken into consideration as it has not been searched and can thus not be examined with respect to its relevance in the context of Articles 33(2) and (3) PCT. Said functional feature is furthermore not in line with the definition of the corresponding method as originally described throughout the description and as claimed in the original claims 1-4 (see e.g. description, page 5, line 21 onwards) which covered both indirect and direct mechanisms leading to the inhibition of the production of pro-inflammatory cytokines in RA synovial tissue.
Attention is again drawn to the fact that only the use of IkappaBalpha and antibodies specific for activated T-cells (not limited to cytokine-activated T-cells) was searched. No further "specific" substances which would actually identify or act upon a precisely defined T cell population such as Tck cells (unambiguously distinguishable from well known T-cell (activated) populations identifiable with the standard surface markers) that would supposedly specifically mediate the production of pro-inflammatory cytokines in RA, have been disclosed in the present application (in this respect, see requirements of Articles 5 and 6 PCT).
It should be noted that this is also the case for the subject-matter of claim 6 which relates to nucleic acid molecules encoding a polypeptide which selectively inhibits Tck cells, such as for instance the above mentioned antibodies (or fragments thereof).

3.2 Thus amended claims 1-6 and 46-48 are considered to lack an inventive step under Article 33(3) PCT for the following reasons:

Document D1 discloses that adenoviral infection with IkappaBalpha inhibits the production of TNFalpha by macrophages in rheumatoid arthritis. Said document does not explicitly describe that patients were actually treated with the above-mentioned substance, but strongly suggests to use the above inhibitor as a therapeutic agent in the present context.

3.3 Document D3, discloses that cytokine stimulation of T lymphocytes regulates their capacity to induce monocyte production of tumour necrosis factor alpha (TNFalpha). Although no experimental data is disclosed in this document, it explicitly suggests a possible relevance in the pathophysiology of RA.
In this respect, the proinflammatory role of TNF is well known, e.g. from D2 which discloses strategies to restrain TNFalpha in e.g RA with various components including NF-kappaB inhibitors, anti-TNFalpha antibodies and various cytokines or synthetic drugs. The skilled person would thus be lead to investigate the possibility of regulating the detrimental TNFalpha production by influencing (by e.g. reducing, inhibiting) the activity of Tck cells on monocytes .

3.3.1

Thus, in the light of D1 combined with D2 and D3, methods for identifying compounds with a desired RA-treatment efficacy, in this case by testing the ability to selectively inhibit Tck cells would appear to be straightforward.
Consequently the subject-matter of claim 7 lacks an inventive step. Claims 8-23 related to said claim 7 concern embodiments which are either known per se or do not appear to contain any additional features which would confer the required inventive step to the said claimed subject-matter. With respect to the subject-matter of claims 21-23 which relate to a method for detecting PI3 kinase activation activity, please see section VIII below).

3.3.2

The same objection applies to the antibodies, methods for making the same, cells expressing the same, methods for identifying the same as well as components containing the same according to claims 25-39 or to the related subject-matter as defined in claims 40 to 44. With respect to antibodies against "activated" T-cells, see e.g. D4-D7 which disclose antibodies against "activated" T cells and in particular D4 which also describes the induction of microglial production of TNF

alpha production by the activated T-cells. This latter document mentions the relevance of its findings in various areas, e.g. inflammatory diseases such as RA. Thus, even if the major objections under Articles 5 and 6 PCT listed in section VIII could be overcome, said embodiments would still lack inventive step in the light of said documents, in combination with any of the documents as cited above.

4. For the assessment of the present claims 1-6,28 and 44-48 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

section VII

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1, D2 and D4-D7 above is not mentioned in the description, nor are these documents identified therein.

section VIII

1. As already mentioned in the Search Report, the inhibitor compounds referred to throughout the claimed subject-matter relate to an extremely large number of possible compounds and the use thereof (see e.g. all the known compounds cited at pages 19 and 20 of the present description as well as the numerous further possibilities cited throughout the application). Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure for a part of said claims.

2. In this context it should be noted that the present description and examples do not give any precise examples of PI3 kinase "activators" (see claims 21-23), but

merely mention "inhibitors" of said enzyme in the context of detection methods for identifying compounds which would have efficacy in the treatment of a chronic inflammatory disease. The number of possibilities covered by the scope of said claims 21-23 is unduly broad (Article 6 PCT) and as no meaningful search could be performed for those parts of claims 21-23 covering said feature, no examination has been performed for said aspect of said claims.
The same remark is valid mutatis mutandis for the compounds and antibodies throughout claims 24-48 (including the claimed nucleic acids encoding antibody/cytotoxin conjugates and claimed vectors and host cell lines related thereto) as the present description or examples do not disclose any compounds or "specific antibodies" which have actually been produced (no hybridomas). The examples merely recite a possible protocol with respect to a production of such antibodies, without however actually describing "produced" or "isolated" antibodies which would have the required specificity for "cytokine activated" T-cells. The required support withing the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT are thus not given. It is for instance also not sure which cytokines, or combination of the same, would have to be used to activate T-cells which would show adequate antigenic determinants showing the required functional features recited in present claim 1 and which would be capable of generating specific antibodies thereto.

3. The term "antibody-**like**" molecule used in the claims is considered to be vague and indefinite (Article 6 PCT).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
KENF/P23194PC		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 00/ 03660	25/09/2000	24/09/1999

Applicant

THE MATHILDA AND TERENCE KENNEDY INSTITUTE OF ...

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 9 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[ ] the text is approved as submitted by the applicant.

[X] the text has been established by this Authority to read as follows:

TREATMENT OF CHRONIC INFLAMMATORY DISEASE BY INHIBITING SUB-GROUPS OF ACTIVATED T-CELLS

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 00/03660

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.: Part of claims 1-3, 6 and 26-50 and whole of claim 5
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/[redacted]00/03660

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/13 C12N15/62 C12N15/06 G01N33/53 G01N33/573
C12Q1/68 C12Q1/37 C07K16/28 A61K38/48 C12N5/12
A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BIOSIS, EPO-Internal, MEDLINE, WPI Data, PAJ, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FOXWELL BRIAN ET AL: "Efficient adenoviral infection with IkappaBalpha reveals that macrophage tumor necrosis factor alpha production in rheumatoid arthritis is NF-kappaB dependent." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 95, no. 14, 7 July 1998 (1998-07-07), pages 8211-8215, XP002098099 July 7, 1998 ISSN: 0027-8424 abstract page 8212, last paragraph -page 8215, paragraph 1	1-4,6,7, 26,47-50
Y		8-25, 27-46

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 March 2001	30.03.01

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Muller-Thomalla, K

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EIGLER A ET AL: "Taming TNF: strategies to restrain this proinflammatory cytokine" IMMUNOLOGY TODAY,GB,ELSEVIER PUBLICATIONS, CAMBRIDGE, vol. 18, no. 10, 1 October 1997 (1997-10-01), pages 487-492, XP004091986 ISSN: 0167-5699 page 489, column 1, paragraph 2 -page 492, column 1, paragraph 2; table 2 ---	8-25, 27-46
Y	SEBBAG M ET AL: "Cytokine stimulation of T lymphocytes regulates their capacity to induce monocyte production of tumor necrosis factor-alpha, but not interleukin-10: possible relevance to pathophysiology of rheumatoid arthritis." EUROPEAN JOURNAL OF IMMUNOLOGY, (1997 MAR) 27 (3) 624-32. , XP000971524 abstract page 625, column 1, last paragraph -page 628, column 1, paragraph 1 page 630, column 1, paragraph 2 -page 631, column 2, paragraph 1 ---	8-22
Y	WARD S G ET AL: "PI 3-kinase: a pivotal pathway in T-cell activation?" IMMUNOLOGY TODAY,GB,ELSEVIER PUBLICATIONS, CAMBRIDGE, vol. 17, no. 4, 1 April 1996 (1996-04-01), pages 187-197, XP004034692 ISSN: 0167-5699 page 190, column 1, last paragraph -page 192, column 1, paragraph 1; figure 1 ---	23-25
Y	BHATTACHARYYA S P ET AL: "Activated T lymphocytes induce degranulation and cytokine production by human mast cells following cell-to-cell contact." JOURNAL OF LEUKOCYTE BIOLOGY, (1998 MAR) 63 (3) 337-41. , XP000971545 abstract page 339, column 2, last paragraph -page 340, column 2, paragraph 1 --- -/--	23-25

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International Application No
PCT/[redacted]00/03660

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHABOT S ET AL: "Microglial production of TNF - alpha is induced by activated T lymphocytes. Involvement of VLA-4 and inhibition by interferonbeta-1b." JOURNAL OF CLINICAL INVESTIGATION, (1997 AUG 1) 100 (3) 604-12. , XP000971530 abstract page 604, column 2, last paragraph -page 605, column 1, paragraph 3 page 605, column 2, last paragraph -page 608, column 1, paragraph 1 page 609, column 1, paragraph 2 -page 611, column 2, paragraph 2 ---	27-46
X	AVICE M N ET AL: "Lymphocyte activation gene-3, a MHC class II ligand expressed on activated T cells, stimulates TNF - alpha and IL-12 production by monocytes and dendritic cells." JOURNAL OF IMMUNOLOGY, (1999 MAR 1) 162 (5) 2748-53. , XP002156054 abstract page 2794, column 2, paragraph 2 -page 2750, column 1, paragraph 2 page 2752, column 1, paragraph 2 -column 2, paragraph 2 ---	27-50
X	US 5 085 985 A (MAINO VERNON C ET AL) 4 February 1992 (1992-02-04) column 7, line 64 -column 12, line 17 ---	27-47
X	MACLEAN J A ET AL: "Anti -CD3: anti - IL - 2 receptor bispecific monoclonal antibody. Targeting of activated T cells in vitro." JOURNAL OF IMMUNOLOGY, (1993 FEB 15) 150 (4) 1619-28. , XP002156055 abstract page 1625, column 2, paragraph 2 -page 1627, column 2, paragraph 3 ---	27-47

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International Application No
PCT/[redacted]00/03660

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LONDEI M ET AL: "Cloning of activated t cells from rheumatoid arthritis joints detection of collagen type ii specific cells." SYMPOSIUM ON MOLECULAR AND CELLULAR MECHANISMS OF HUMAN HYPERSENSITIVITY AND AUTOIMMUNITY HELD AT THE 17TH ANNUAL UCLA (UNIVERSITY OF CALIFORNIA-LOS ANGELES) SYMPOSIA ON MOLECULAR AND CELLULAR BIOLOGY, KEYSTONE, COLORADO, USA, APRIL 17-23, 1988. J CE, XP000971527 ✓ abstract ---	51-55
X	COHEN S B ET AL: "High level of interleukin-10 production by the activated T cell population within the rheumatoid synovial membrane." ARTHRITIS AND RHEUMATISM, (1995 JUL) 38 (7) 946-52. , ✓ XP000971529 page 946, column 1, line 1 -column 2, paragraph 2 page 947, column 1, paragraph 3 -page 948, column 1, paragraph 1 table 1 page 951, column 1, last paragraph -page 952, column 1, paragraph 2 ---	51-55
X	EP 0 896 999 A (SHIONOGI & CO) 17 February 1999 (1999-02-17) page 6, line 31 -page 7, line 55; claims 1-8 ---	51-55
A	MCINNES I B ET AL: "Interleukin 15: a proinflammatory role in rheumatoid arthritis synovitis" IMMUNOLOGY TODAY,GB,ELSEVIER PUBLICATIONS, CAMBRIDGE, vol. 19, no. 2, 1 February 1998 (1998-02-01), pages 75-79, XP004107030 ISSN: 0167-5699 the whole document -----	51-55

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 1-4,6,7,49 and 50 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
Although claims 8-10, 13-15,23-25 (insofar as they relate to an in vivo method) are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.2

Claims Nos.: Part of claims 1-3, 6 and 26-50 and whole of claim 5

Present claims 1-3, 6 and 26-50 relate to an extremely large number of possible compounds and the use thereof (see e.g. all the known compounds cited at pages 19 and 20 of the present description as well as the numerous further possibilities cited throughout the application). Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the use of the compounds as defined in claims 4 and 7 and as used in the examples.
In this context it should be noted that the present description and examples do not give any precise examples of PI3 kinase "activators", but merely mentions "inhibitors" of said enzyme in the context of detection methods for identifying compounds which would have efficacy in the treatment of a chronic inflammatory disease. Said claim 5 has thus not been searched as the number of possibilities covered by the scope of said claim is unduly broad not allowing a meaningful search to be performed.

The same remark is valid mutatis mutandis for the antibodies throughout claims 26-50 (including the claimed nucleic acids encoding antibody/cytotoxin conjugates and claimed vectors and host cell lines related thereto) as the present description or examples do not disclose any "specific antibodies" which have actually been produced (no hybridomas). The examples merely recite a possible protocol with respect to a production of such antibodies, without however actually describing "produced" or "isolated" antibodies which would have the required specificity for "cytokine activated" T-cells. The required support withing the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT are thus not given. It is for instance also not sure which cytokines, or combination of the same, would have to be used to activate T-cells which would show adequate antigenic determinants identifiable by specific antibodies.
Thus only antibodies which are specific for "activated T-cells" (irrespective of their mode of activation) in general have been searched in the given context.

The applicant's attention is drawn to the fact that claims, or parts of

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 1-4,6,7,49 and 50 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
Although claims 8-10, 13-15,23-25 (insofar as they relate to an in vivo method) are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.2

Claims Nos.: Part of claims 1-3, 6 and 26-50 and whole of claim 5

Present claims 1-3, 6 and 26-50 relate to an extremely large number of possible compounds and the use thereof (see e.g. all the known compounds cited at pages 19 and 20 of the present description as well as the numerous further possibilities cited throughout the application). Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the use of the compounds as defined in claims 4 and 7 and as used in the examples.
In this context it should be noted that the present description and examples do not give any precise examples of PI3 kinase "activators", but merely mentions "inhibitors" of said enzyme in the context of detection methods for identifying compounds which would have efficacy in the treatment of a chronic inflammatory disease. Said claim 5 has thus not been searched as the number of possibilities covered by the scope of said claim is unduly broad not allowing a meaningful search to be performed.

The same remark is valid mutatis mutandis for the antibodies throughout claims 26-50 (including the claimed nucleic acids encoding antibody/cytotoxin conjugates and claimed vectors and host cell lines related thereto) as the present description or examples do not disclose any "specific antibodies" which have actually been produced (no hybridomas). The examples merely recite a possible protocol with respect to a production of such antibodies, without however actually describing "produced" or "isolated" antibodies which would have the required specificity for "cytokine activated" T-cells. The required support withing the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT are thus not given. It is for instance also not sure which cytokines, or combination of the same, would have to be used to activate T-cells which would show adequate antigenic determinants identifiable by specific antibodies.
Thus only antibodies which are specific for "activated T-cells" (irrespective of their mode of activation) in general have been searched in the given context.

The applicant's attention is drawn to the fact that claims, or parts of

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: Part of claims 1-4,6-50

   Method of treatment of a chronic inflammatory disease in a patient comprising the administration of a compound that selectively inhibits cytokine-activated T cells (designated Tck by the Applicant). Methods for identifying said compounds as well as the compounds per se.

2. Claims: 51-55

   A preparation of T-cell enriched cells wherein the cells are from tissue from a site of inflammation in a patient suffering from a chronic inflammatory disease.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 00/03660

Box I Observations wher certain claims were found unsearchable (Continuation f item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.: Part of claims 1-3, 6 and 26-50 and whole of claim 5
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/[redacted]00/03660

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5085985 A	04-02-1992	NONE	
EP 0896999 A	17-02-1999	AU 711303 B	07-10-1999
		AU 1939897 A	01-10-1997
		CA 2249023 A	18-09-1997
		CN 1218506 A	02-06-1999
		WO 9733977 A	18-09-1997

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 March 2001 (29.03.2001)

PCT

(10) International Publication Number
WO 01/21202 A3

(51) International Patent Classification[7]: C12N 15/13, 15/62, 15/06, G01N 33/53, 33/573, C12Q 1/68, 1/37, C07K 16/28, A61K 38/48, C12N 5/12, A61K 47/48

(21) International Application Number: PCT/GB00/03660

(22) International Filing Date:
25 September 2000 (25.09.2000)

(25) Filing Language: English

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(30) Priority Data:
9922505.4 24 September 1999 (24.09.1999) GB

(71) Applicant *(for all designated States except US)*: **THE MATHILDA AND TERENCE KENNEDY INSTITUTE OF RHEUMATOLOGY** [GB/GB]; 1 Aspenlea Road, Hammersmith, London W6 8LH (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BRENNAN, Fionula, Mary** [AU/GB]; The Mathilda and Terence Kennedy Institute of Rheu, matology, 1 Aspenlea Road, Hammersmith, London W6 8LH (GB). **FELDMANN, Marc** [AU/GB]; The Mathilda and Terence Kennedy Institute of Rheu, matology, 1 Aspenlea Road, Hammersmith, London W6 8LH (GB). **FOXWELL, Brian, Maurice, John** [GB/GB]; The Mathilda and Terence Kennedy Institute of Rheu, matology, 1 Aspenlea Road, Hammersmith, London W6 8LH (GB).

(74) Agent: **BASSETT, Richard, S.**; Eric Potter Clarkson, Park View House, 58 The Ropewalk, Nottingham NG1 5DD (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
11 October 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: TREATMENT OF CHRONIC INFLAMMATORY DISEASE BY INHIBITING SUB-GROUPS OF ACTIVATED T-CELLS

(57) Abstract: The invention provides a method of treatment of a chronic inflammatory disease (such as rheumatoid arthritis) in a patient, the method comprising the administration to the patient of a compound that selectively inhibits T_{ck} cells. Preferably, said compound selectively inhibits T_{ck} cell-induced release of one or more pro-inflammatory cytokines from monocytes. Advantageously, said compound inhibits NF-κB. Conveniently, said compound activates PI3 kinase. The invention further provides a method of identifying a compound with efficacy in the treatment of a chronic inflammatory disease comprising the step of testing said compound for an ability to selectively inhibit T_{ck} cells. Preferably, said method of identifying a compound with efficacy in the treatment of a chronic inflammatory disease comprises the step of testing said compound for an ability to selectively inhibit T_{ck} cell-induced release of one or more pro-inflammatory cytokines from monocytes. Conveniently, the pro-inflammatory cytokine is tumour necrosis factor α (TNFα). The invention further provides compounds identifiable or identified by said methods and the use of said compounds in medicine. Additionally, the invention provides an antibody-like molecule with specificity for T_{ck} cells, and compounds comprising said antibody-like molecule and a cytotoxic moiety.

WO 01/21202 A3

INTERNATIONAL SEARCH REPORT

Inter...ional Application No
PCT/GB 00/03660

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/13 C12N15/62 C12N15/06 G01N33/53 G01N33/573
C12Q1/68 C12Q1/37 C07K16/28 A61K38/48 C12N5/12
A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BIOSIS, EPO-Internal, MEDLINE, WPI Data, PAJ, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FOXWELL BRIAN ET AL: "Efficient adenoviral infection with IkappaBalpha reveals that macrophage tumor necrosis factor alpha production in rheumatoid arthritis is NF-kappaB dependent." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 95, no. 14, 7 July 1998 (1998-07-07), pages 8211-8215, XP002098099 July 7, 1998 ISSN: 0027-8424 abstract page 8212, last paragraph -page 8215, paragraph 1	1-4,6,7, 26,47-50
Y	--- -/--	8-25, 27-46

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 March 2001	30.03.01

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Muller-Thomalla, K

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED [redacted] RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EIGLER A ET AL: "Taming TNF: strategies to restrain this proinflammatory cytokine" IMMUNOLOGY TODAY,GB,ELSEVIER PUBLICATIONS, CAMBRIDGE, vol. 18, no. 10, 1 October 1997 (1997-10-01), pages 487-492, XP004091986 ISSN: 0167-5699 page 489, column 1, paragraph 2 -page 492, column 1, paragraph 2; table 2 ---	8-25, 27-46
Y	SEBBAG M ET AL: "Cytokine stimulation of T lymphocytes regulates their capacity to induce monocyte production of tumor necrosis factor-alpha, but not interleukin-10: possible relevance to pathophysiology of rheumatoid arthritis." EUROPEAN JOURNAL OF IMMUNOLOGY, (1997 MAR) 27 (3) 624-32. , XP000971524 abstract page 625, column 1, last paragraph -page 628, column 1, paragraph 1 page 630, column 1, paragraph 2 -page 631, column 2, paragraph 1 ---	8-22
Y	WARD S G ET AL: "PI 3-kinase: a pivotal pathway in T-cell activation?" IMMUNOLOGY TODAY,GB,ELSEVIER PUBLICATIONS, CAMBRIDGE, vol. 17, no. 4, 1 April 1996 (1996-04-01), pages 187-197, XP004034692 ISSN: 0167-5699 page 190, column 1, last paragraph -page 192, column 1, paragraph 1; figure 1 ---	23-25
Y	BHATTACHARYYA S P ET AL: "Activated T lymphocytes induce degranulation and cytokine production by human mast cells following cell-to-cell contact." JOURNAL OF LEUKOCYTE BIOLOGY, (1998 MAR) 63 (3) 337-41. , XP000971545 abstract page 339, column 2, last paragraph -page 340, column 2, paragraph 1 --- -/--	23-25

6

C.(Continuation) DOCUMENTS CONSIDERED [illegible] RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHABOT S ET AL: "Microglial production of TNF - alpha is induced by activated T lymphocytes. Involvement of VLA-4 and inhibition by interferonbeta-1b." JOURNAL OF CLINICAL INVESTIGATION, (1997 AUG 1) 100 (3) 604-12. , XP000971530 abstract page 604, column 2, last paragraph -page 605, column 1, paragraph 3 page 605, column 2, last paragraph -page 608, column 1, paragraph 1 page 609, column 1, paragraph 2 -page 611, column 2, paragraph 2 ---	27-46
X	AVICE M N ET AL: "Lymphocyte activation gene-3, a MHC class II ligand expressed on activated T cells, stimulates TNF - alpha and IL-12 production by monocytes and dendritic cells." JOURNAL OF IMMUNOLOGY, (1999 MAR 1) 162 (5) 2748-53. , XP002156054 abstract page 2794, column 2, paragraph 2 -page 2750, column 1, paragraph 2 page 2752, column 1, paragraph 2 -column 2, paragraph 2 ---	27-50
X	US 5 085 985 A (MAINO VERNON C ET AL) 4 February 1992 (1992-02-04) column 7, line 64 -column 12, line 17 ---	27-47
X	MACLEAN J A ET AL: "Anti -CD3: anti - IL - 2 receptor bispecific monoclonal antibody. Targeting of activated T cells in vitro." JOURNAL OF IMMUNOLOGY, (1993 FEB 15) 150 (4) 1619-28. , XP002156055 abstract page 1625, column 2, paragraph 2 -page 1627, column 2, paragraph 3 --- -/--	27-47

C.(Continuation) DOCUMENTS CONSIDERED RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LONDEI M ET AL: "Cloning of activated t cells from rheumatoid arthritis joints detection of collagen type ii specific cells." SYMPOSIUM ON MOLECULAR AND CELLULAR MECHANISMS OF HUMAN HYPERSENSITIVITY AND AUTOIMMUNITY HELD AT THE 17TH ANNUAL UCLA (UNIVERSITY OF CALIFORNIA-LOS ANGELES) SYMPOSIA ON MOLECULAR AND CELLULAR BIOLOGY, KEYSTONE, COLORADO, USA, APRIL 17-23, 1988. J CE, XP000971527 abstract ---	51-55
X	COHEN S B ET AL: "High level of interleukin-10 production by the activated T cell population within the rheumatoid synovial membrane." ARTHRITIS AND RHEUMATISM, (1995 JUL) 38 (7) 946-52. , XP000971529 page 946, column 1, line 1 -column 2, paragraph 2 page 947, column 1, paragraph 3 -page 948, column 1, paragraph 1 table 1 page 951, column 1, last paragraph -page 952, column 1, paragraph 2 ---	51-55
X	EP 0 896 999 A (SHIONOGI & CO) 17 February 1999 (1999-02-17) page 6, line 31 -page 7, line 55; claims 1-8 ---	51-55
A	MCINNES I B ET AL: "Interleukin 15: a proinflammatory role in rheumatoid arthritis synovitis" IMMUNOLOGY TODAY,GB,ELSEVIER PUBLICATIONS, CAMBRIDGE, vol. 19, no. 2, 1 February 1998 (1998-02-01), pages 75-79, XP004107030 ISSN: 0167-5699 the whole document -----	51-55

6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 00/03660

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.: Part of claims 1-3, 6 and 26-50 and whole of claim 5
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 1-4,6,7,49 and 50 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
Although claims 8-10, 13-15,23-25 (insofar as they relate to an in vivo method) are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.2

Claims Nos.: Part of claims 1-3, 6 and 26-50 and whole of claim 5

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In this context it should be noted that the present description and examples do not give any precise examples of PI3 kinase "activators", but merely mentions "inhibitors" of said enzyme in the context of detection methods for identifying compounds which would have efficacy in the treatment of a chronic inflammatory disease. Said claim 5 has thus not been searched as the number of possibilities covered by the scope of said claim is unduly broad not allowing a meaningful search to be performed.

The same remark is valid mutatis mutandis for the antibodies throughout claims 26-50 (including the claimed nucleic acids encoding antibody/cytotoxin conjugates and claimed vectors and host cell lines related thereto) as the present description or examples do not disclose any "specific antibodies" which have actually been produced (no hybridomas). The examples merely recite a possible protocol with respect to a production of such antibodies, without however actually describing "produced" or "isolated" antibodies which would have the required specificity for "cytokine activated" T-cells. The required support withing the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT are thus not given. It is for instance also not sure which cytokines, or combination of the same, would have to be used to activate T-cells which would show adequate antigenic determinants identifiable by specific antibodies.
Thus only antibodies which are specific for "activated T-cells" (irrespective of their mode of activation) in general have been searched in the given context.

The applicant's attention is drawn to the fact that claims, or parts of

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: Part of claims 1-4,6-50

Method of treatment of a chronic inflammatory disease in a patient comprising the administration of a compound that selectively inhibits cytokine-activated T cells (designated Tck by the Applicant). Methods for identifying said compounds as well as the compounds per se.

2. Claims: 51-55

A preparation of T-cell enriched cells wherein the cells are from tissue from a site of inflammation in a patient suffering from a chronic inflammatory disease.

Information on patent family members

Inter[illegible]nal Application No
PCT/GB 00/03660

Patent document cited in search report		[illegible]ication date	Patent family member(s)		Publication date
US 5085985	A	04-02-1992	NONE		
EP 0896999	A	17-02-1999	AU	711303 B	07-10-1999
			AU	1939897 A	01-10-1997
			CA	2249023 A	18-09-1997
			CN	1218506 A	02-06-1999
			WO	9733977 A	18-09-1997

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date.

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* KENF / P23194PC

Box No. I **TITLE OF INVENTION**

THERAPEUTIC METHODS AND COMPOUNDS

Box No. II **APPLICANT**

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

The Mathilda and Terence Kennedy Institute of Rheumatology
1 Aspenlea Road
Hammersmith
London
W6 8LH
United Kingdom

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III **FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)**

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BRENNAN, Fionula Mary
The Mathilda and Terence Kennedy Institute of Rheumatology
1 Aspenlea Road
Hammersmith
London
W6 8LH
United Kingdom

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(if this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: AU

State *(that is, country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV **AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE**

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Bassett, Richard S
Eric Potter Clarkson
Park View House
58 The Ropewalk
Nottingham. NG1 5DD
GB

Telephone No. (0115) 9552211

Facsimile No (0115) 9552201

Teleprinter No. 37540 Potter G

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
FELDMANN, Marc
The Mathilda and Terence Kennedy Institute of Rheumatology
1 Aspenlea Road
Hammersmith
London
W6 8LH
United Kingdom

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(if this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: AU

State *(that is, country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated states ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
FOXWELL, Brian Maurice John
The Mathilda and Terence Kennedy Institute of Rheumatology
1 Aspenlea Road
Hammersmith
London
W6 8LH
United Kingdom

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(if this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated states ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
☐ applicant only
☐ applicant and inventor
☐ inventor only *(if this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated states ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
☐ applicant only
☐ applicant and inventor
☐ inventor only *(if this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated states ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- [X] **AP** **ARIPO Patent: GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SL** Sierra Leone, **SZ** Swaziland, **TZ** United Republic of Tanzania, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- [X] **EA** **Eurasian Patent: AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- [X] **EP** **European Patent: AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- [X] **OA** **OAPI Patent: BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea-Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- [X] **AE** United Arab Emirates
- [X] **AL** Albania .....
- [X] **AM** Armenia .....
- [X] **AT** Austria .....
- [X] **AU** Australia .....
- [X] **AZ** Azerbaijan
- [X] **BA** Bosnia and Herzegovina .....
- [X] **BB** Barbados
- [X] **BG** Bulgaria .....
- [X] **BR** Brazil .....
- [X] **BY** Belarus .....
- [X] **CA** Canada
- [X] **CH and LI** Switzerland and Liechtenstein
- [X] **CN** China .....
- [X] **CR** Costa Rica .....
- [X] **CU** Cuba .....
- [X] **CZ** Czech Republic .....
- [X] **DE** Germany .....
- [X] **DK** Denmark .....
- [X] **DM** Dominica
- [X] **EE** Estonia .....
- [X] **ES** Spain .....
- [X] **FI** Finland .....
- [X] **GB** United Kingdom
- [X] **GD** Grenada
- [X] **GE** Georgia .....
- [X] **GH** Ghana .....
- [X] **GM** Gambia
- [X] **HR** Croatia .....
- [X] **HU** Hungary .....
- [X] **ID** Indonesia
- [X] **IL** Israel .....
- [X] **IN** India .....
- [X] **IS** Iceland
- [X] **JP** Japan .....
- [X] **KE** Kenya .....
- [X] **KG** Kyrgyzstan .....
- [X] **KP** Democratic People's Republic of Korea .....
- [X] **KR** Republic of Korea .....
- [X] **KZ** Kazakhstan .....
- [X] **LC** Saint Lucia
- [X] **LK** Sri Lanka
- [X] **LR** Liberia
- [X] **LS** Lesotho .....
- [X] **LT** Lithuania
- [X] **LU** Luxembourg
- [X] **LV** Latvia
- [X] **MA** Morocco .....
- [X] **MD** Republic of Moldova .....
- [X] **MG** Madagascar .....
- [X] **MK** The former Yugoslav Republic of Macedonia .....
- [X] **MN** Mongolia
- [X] **MW** Malawi .....
- [X] **MX** Mexico .....
- [X] **NO** Norway
- [X] **NZ** New Zealand .....
- [X] **PL** Poland .....
- [X] **PT** Portugal .....
- [X] **RO** Romania
- [X] **RU** Russian Federation .....
- [X] **SD** Sudan
- [X] **SE** Sweden
- [X] **SG** Singapore
- [X] **SI** Slovenia .....
- [X] **SK** Slovakia .....
- [X] **SL** Sierra Leone
- [X] **TJ** Tajikistan .....
- [X] **TM** Turkmenistan .....
- [X] **TR** Turkey .....
- [X] **TT** Trinidad and Tobago .....
- [X] **TZ** United Republic of Tanzania .....
- [X] **UA** Ukraine .....
- [X] **UG** Uganda .....
- [X] **US** United States of America .....
- [X] **UZ** Uzbekistan .....
- [X] **VN** Viet Nam .....
- [X] **YU** Yugoslavia .....
- [X] **ZA** South Africa .....
- [X] **ZW** Zimbabwe .....

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

- [X] **DZ** Algeria .....
- [X] **AG** Antigua and Barbuda .....
- [X] **BZ** Belize
- [X] **MZ** Mozambique

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of*

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is: National application: Country	regional application:* regional Office	international application: receiving Office
item (1) 24 September 1999 (24/09/1999)	9922505.4	GB		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): (1)

** Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*: ISA /

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*:

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	:	4
description (excluding sequence listing part)	:	79
claims	:	9
abstract	:	1
drawings	:	9
sequence listing part of description	:	0
Total number of sheets	:	102

This international application is **accompanied by** the item(s) marked below:

1. ☐ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☒ other *(specify)*: Form 23/77

Figure of the drawings which should accompany the abstract: 1

Language of filing of the International application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Richard S Bassett

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	☐ received:
4. Date of timely receipt of the required corrections under PCT Article 11(2):	☐ not received:
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
BASSETT, Richard, S.
Eric Potter Clarkson
Park View House
58 The Ropewalk
Nottingham NG1 5DD
ROYAUME-UNI

File

IMPORTANT NOTICE

Date of mailing (day/month/year)		
29 March 2001 (29.03.01)		
Applicant's or agent's file reference		
KENF/P23194PC		
International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/GB00/03660	25 September 2000 (25.09.00)	24 September 1999 (24.09.99)
Applicant		
THE MATHILDA AND TERENCE KENNEDY INSTITUTE OF RHEUMATOLOGY et al		

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,KP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AG,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,BZ,CA,CH,CN,CR,CU,CZ,DE,DK,DM,DZ,EA,EE,EP,ES, FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK, MN,MW,MX,MZ,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   29 March 2001 (29.03.01) under No. WO 01/21202

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a **demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 28 June 2001 (28.06.01)	
International application No. PCT/GB00/03660	**Applicant's or agent's file reference** KENF/P23194PC
International filing date (day/month/year) 25 September 2000 (25.09.00)	**Priority date** (day/month/year) 24 September 1999 (24.09.99)
Applicant BRENNAN, Fionula, Mary et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

18 April 2001 (18.04.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Juan Cruz
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

BASSETT, Richard, S.
Eric Potter Clarkson
Park View House
58 The Ropewalk
Nottingham NG1 5DD
ROYAUME-UNI

Date of mailing (day/month/year) 15 April 2002 (15.04.02)	
Applicant's or agent's file reference KENF/P23194PC	**IMPORTANT NOTIFICATION**
International application No. PCT/GB00/03660	**International filing date** (day/month/year) 25 September 2000 (25.09.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
THE MATHILDA AND TERENCE KENNEDY INSTITUTE OF RHEUMATOLOGY TRUST 1 Aspenlea Road Hammersmith London W6 8LH United Kingdom	GB	GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
SYNOVIS LIMITED 90 Fetter Lane London EC4A 1JP United Kingdom	GB	GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Lazar Joseph PANAKAL
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38